II. Rejections Under 35 U.S.C. § 112, Second Paragraph

A. Rejection of Claims 11, 23, 35, 40, and 42-44

Claims 11, 23, 35, 40, and 42-44 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Office Action at pages 2-3. Applicants respectfully traverse this ground for rejection.

The claims were rejected for allegedly failing "to correspond in scope with that which applicant(s) regard as the invention." In support of this ground for rejection, the examiner stated that the application did not provide support for a "liquid dispersion [which] is not limited to water," as the application is allegedly limited to water-insoluble drugs. Applicants courteously disagree with the Examiner's analysis and conclusion.

Applicants' claimed invention is directed to nanoparticulate "insoluble drugs." Such drugs can be can be made by milling in any medium in which the drug is poorly soluble. This is also described in U.S. Patent No. 6,145,684, which was specifically incorporated by reference into the present application (*see e.g.*, page 7, lines 9-11):

> A preferred liquid dispersion medium is water. However, the invention can be practiced with other liquid media in which a drug substance is poorly soluble and dispersible, including, for example, aqueous salt solutions, safflower oil, and solvents such as ethanol , t-butanol, hexane, and glycol.

See col. 3, lines 45-50, of U.S. Patent No. 5,145,684 (EXHIBIT 1).

Moreover, the present application also specifically describes milling of poorly soluble compounds in "a non-aqueous, non-pressurized milling system," using "a non-aqueous liquid which has a vapor pressure of 1 atm or less at room temperature." *See* page 10, lines 16-21, of the application (emphasis added). An exemplary non-aqueous milling media is, for example, a high boiling point halogenated hydrocarbon. *See* page 10, lines 19-20, of the application. Exemplary non-aqueous liquids include ethanol, CFC-11, and CFC-114. *See* page 19, lines 17-18, of the application.

Finally, the application describes milling in a pressurized system using a non-aqueous liquid which has a vapor pressure of more than 1 atm at room temperature. Such liquids can be,

for example, a halogenated hydrocarbon propellant which has a low boiling point. *See* page 10, lines 22-28, of the application.

For at least these reasons, it is respectfully submitted that the claims are not limited to "water-insoluble" drugs and, therefore, the claims are commensurate in scope with Applicants' disclosure. This ground for rejection should be withdrawn.

B. Rejection of Claims 65-70

Claims 65-70 were rejected under 35 U.S.C. § 112, second paragraph, for allegedly lacking antecedent basis. These claims were amended to recite proper antecedent basis. Accordingly, this ground for rejection is moot.

III. Rejections under 35 U.S. §§ 102 (e) and 103(a)

Claims 11-14, 16-25, 27-33, 40 , 41, 44, 45, 59-62, 69-71, 73, 75, 77, 79, 81, 90, 92-95, 111, and 113-116 were rejected as being allegedly anticipated by Edwards et al., U.S. Patent No. 5,985,309, for "Preparation of Particles for Inhalation." Office Action at page 4. Applicants respectfully traverse this ground for rejection.

In addition, claims 11-34, 40, 41, 44, 45, 47, 48, 51-58, 59-62, 69-82, 90-96, and 111-117 were rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Edwards et al. Office Action at pages 7-8. Applicants respectfully traverse this ground for rejection.

A. The Preamble of the Claims Recites Claim Limitations Which Should be Given Patentable Weight

Claims 11, 23, 40, and 44 were first rejected as the claim limitations were not given patentable weight since "the recitation occurs in the preamble." Office Action at page 4. In support of this ground for rejection, the examiner stated that a preamble is not given patentable weight when "it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness." Office Action at page 4. Applicants respectfully disagree.

The language in the preamble of the rejected claims does not merely recite "a purpose or intended use." However, for the sole purpose of advancing the prosecution of this case, claims

11, 23, 35, 40, 42, 43, and 44 were amended to incorporate the limitations in the preamble of the claims into the body of the claims.

B. In Contrast to the Claimed Invention, Edwards et al. Do Not Teach Compositions of Particles Having a Geometric Diameter of Less than About 1 Micron

Applicants claimed invention recites aerosol compositions comprising drug particles having a particle size of less than about 1 micron, *i.e.,* less than about 1000 nm. This is not taught or suggested by Edwards et al.

1. The Examiner Incorrectly Calculated the Geometric Diameter of the Aerosol Particles of Edwards et al.

The Examiner stated that the geometric diameter of the aerosol particles of Edwards et al. have a size of "1.6 μm to 8 μm". Office Action at page 5. The Examiner calculated this number by using Edwards et al.'s disclosed aerodynamic diameter of 1 to 5 μm and the "tap density of 0.4 g/cm^3" of the particles plugged into the following formula:

$$\text{Aerodynamic diameter} = \text{geometric diameter} \, (\text{density})^{1/2}$$

This calculation is incorrect for several reasons. First, Edwards et al. **specifically state** that the geometric diameter of its aerosol particles is from 5 to 30 microns, and **not** "1.6 μm to 8 μm." Second, this calculation is incorrect because "tap density" is not the same as true density, defined as the mass of an object divided by the volume taken up by an object, and which is the term properly used in the equation above. "Tap density" refers to the "packed" density of a dry powder composition which has been "tapped" to settle the contents in a container under specified conditions. Traditional methods of determining tap density involve repeatedly lifting and dropping a container of sample to tap down the volume and pack the particles. *See e.g.*, "Test Method B527-93(2000)e1 Standard Test Method for Determination of Tap Density of Metallic Powders and Compounds," http://www.astm.org/DATABASE.CART/PAGES/ B527.htm (EXHIBIT 2); "Autotap and Dual Autotap," http://www.quantachrome.com/Density/ Autotap.htm (EXHIBIT 3); and "Optimal Tapped Density Tester," http://optimalcontrol.com/ tapped.html (EXHIBIT 4). Therefore, the Examiner's calculation of the geometric particle size

is incorrect, as the examiner used tap density to calculate the geometric particle size rather than the true particle density.

The use of true density in this formula is also evident from a publication by the inventors: Edwards et al., "Large Porous Particles for Pulmonary Drug Delivery Science," *276*:1868-1871 (June 20, 1997) (EXHIBIT 5).

Finally, even if Edwards et al. taught particles having a geometric diameter of "1.6 microns" (which it doesn't), this particle size is **not** "less than about 1 micron," which is the drug particle size required by Applicants' claims. Specifically, a particle size of "1.6 microns" is **60%** greater than a size of "less than about 1 micron."

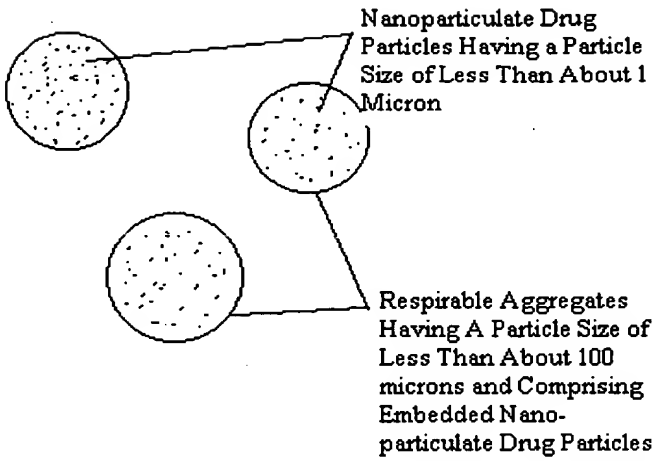
2. The Examiner Incorrectly Stated that Edwards et al.'s Geometric Particle Size of 5 to 30 Microns Reads on Applicants' Particle Size of Less than 100 Microns

Applicants' claimed compositions recite nanoparticulate drug particles having a size of less than about 1 micron, which form aggregates having a diameter of less than about 100 microns. The Examiner concluded that Edwards et al. reads on the claimed invention because:

> [The aerosol particles of Edwards et al. have] a mean diameter of between 5 μm and 30 μm (reading on applicants' less than 100 μm limitation) effective to yield an aerodynamic diameter . . . of the particles of between approximately one and five microns.

Office Action at page 5.

This analysis is incorrect because it fails to recognize the claimed drug particle size of the drug particles comprising the dried powder aggregates. Specifically, the dry powder aggregates have a claimed particle size of less than about 100 microns, while the component drug particles comprising the dry powder aggregates have a particle size of less than about 1 micron, as graphically represented below.



This distinction is significant as the nanoparticulate particle size of the component drug particles results in dramatically superior benefits as compared to prior art aerosol compositions. For example, the claimed dry powder aerosols comprising nanoparticulate drugs result in an increase in the number of drug particles per unit dose and a consequent distribution of the nanoparticulate drug particles over a larger physiological surface area as compared to the same quantity of delivered micronized drug. For systemic delivery via the pulmonary route, this approach takes maximum advantage of the extensive surface area presented in the alveolar region – thus producing more favorable drug delivery profiles, such as a more complete absorption and rapid onset of action.

Moreover, the aerosol compositions of the present invention enable rapid nasal delivery. Nasal delivery of such aerosol compositions will be absorbed more rapidly and completely than micronized aerosol compositions because the nanoparticulate drug particles will dissolve before being cleared by the mucociliary mechanism.

For at least the foregoing reasons it is respectfully submitted that the claimed invention is patentable over Edwards et al. and, therefore, withdrawal of this ground for rejection is courteously requested.

D. Rejections under 35 U.S.C. § 103

A. Rejection of the Claims over Adjei et al. in view of Liversidge et al.

Claims 42, 43, and 97-110 were rejected under 35 U.S.C. § 103 over Adjei et al. in view of Liversidge et al. Office Action at page 6. Applicants respectfully traverse this ground for rejection.

1. The Examiner's Basis for the Rejection

In support of this ground for rejection, the Examiner stated that it would have been obvious to one of ordinary skill in the art to combine the teachings of Adjei et al. and Liversidge et al. to obtain the claimed invention because Adjei et al. allegedly teach "the same method" as claimed by Applicants' "until the desired particle size is obtained." Office Action at page 6. The Examiner then concluded that "Adjei et al. meet the limitations of applicants' claim 42." Office Action at page 6.

Continuing, the Examiner stated that Liversidge et al. was relied upon to teach that it was known in the art "that pressures are altered in milling processes . . ." Office Action at page 6.

2. Adjei et al. Teach Away From Applicants' Claimed Invention, as the Reference Teaches Milling in a Propellant Medium, While the Claimed Invention Requires Evaporation of the Milling Medium Followed by Formulation of the Milled Dry Powder into an Aerosol

Applicants' claims 42 and 43 (and dependent claims 97-110) recite methods of making dry powder aerosols comprising:

(1) milling under non-pressurized (claim 42) or pressurized (claim 43) conditions in a non-aqueous medium to obtain a nanoparticulate drug composition;

(2) evaporating the non-aqueous medium to obtain a dry powder of drug and surface modifier particles; and

(3) formulating the dry powder into an aerosol.

The claimed methods therefore require three distinct steps. Adjei et al. teach away from Applicants' claimed invention, as in contrast this reference teaches a method of "milling the solid components of the formulation directly in the material which serves as the propellant in the final aerosol formulation." *See* page 2, lines 28-29, of Adjei et al. According to Adjei et al., this

one-step method "eliminates the need for the use of a distinct liquid milling medium which must be removed before mixing the solids components of the aerosol formulation with the propellant." *See* page 2, lines 30-32, of Adjei et al. Adjei et al. further teach that the described one-step process is preferred as it "does not involve removing any material added during the process steps...each ingredient added to the aerosol formulations during processing becomes a part of the final formulation and is present in the final formulation."

Thus, Adjei et al. teach away from Applicants' claimed invention, which requires removal of the milling medium prior to formulating the dispersion into an aerosol composition. As Liversidge et al. does not remedy this deficiency of Adjei et al., withdrawal of this ground for rejection is respectfully requested.

B. Rejection of the Claims over Edwards et al. in view of Smith et al.

Claims 11-36, 40 , 41, 44, 45, 47-49, 51-64, 69-96, and 111-117 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Edwards et al. in combination with Smith et al. (U.S. Patent No. 5,785,049). Office Action at page 8. Applicants respectfully traverse this ground for rejection.

In support of this ground for rejection the Examiner stated that "Applicants argue that Edwards et al. do not disclose the use of nanoparticulate drugs in dry powder aerosol compositions . . . [and that] applicants are arguing a limitation from the preamble." Office Action at page 8.

The limitations from the preamble of independent claims 11, 23, 35, 40, 42, 43, and 44 have been incorporated into the body of the claims. Moreover, even before Applicants amended these claims, the body of the claims recited compositions having **nanoparticulate** drug particles, which are not taught or suggested by Edwards et al. or Smith et al.

As discussed above, the benefits of the nanoparticulate drug aerosol compositions claimed by Applicants include more efficient delivery to the deep lung, more favorable drug delivery profiles, such as a more complete absorption and rapid onset of action, and more rapid and complete absorption of aerosols delivered nasally.

For at least the foregoing reasons it is respectfully submitted that the claimed invention is patentable over Edwards et al. in view of Smith et al. and, therefore, withdrawal of this ground for rejection is courteously requested.

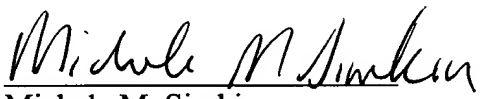
IV. CONCLUSION

Applicants respectfully request reconsideration of this application in view of the above amendments and remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

Should the Examiner have any questions or comments regarding the pending application or this Amendment, the Examiner is requested to call the undersigned at 202-672-5538.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,



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Marked-Up Copy of the Amended Claims

11. (Twice Amended) [A spray-dried powder] An aerosol composition comprising [aggregates of nanoparticulate drug particles, wherein]:

(a) aggregates of a spray-dried powder comprising nanoparticulate drug particles, wherein the nanoparticulate drug particles:

(i) comprise a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml,

(ii) have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(iii) have a surface modifier adsorbed on the surface thereof; and

(b) the aggregates of spray-dried drug particles are less than or equal to about 100 microns in diameter,

wherein the dry powder aggregates are formulated into an aerosol composition.

23. (Twice Amended) [A freeze-dried powder] An aerosol composition comprising [aggregates of nanoparticulate drug particles, wherein]:

(a) [the] aggregates of a freeze-dried drug powder comprising nanoparticulate drug particles, wherein the aggregates of freeze-dried drug are less than or equal to about 100 microns in diameter and [; (b)] the nanoparticulate drug particles:

(i) comprise a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml,

(ii) have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(iii) have a surface modifier adsorbed on the surface thereof,

wherein the freeze-dried powder aggregates are formulated into an aerosol composition.

freeze-dry is diff b/c cl. 11 + nothing about aggregates

35. (Twice Amended) [A dry powder nanoparticulate] An aerosol composition for use in a propellant-based pMDI comprising:

(a) dry powder aggregates of a nanoparticulate poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in at least one liquid dispersion medium of less than about 10 mg/ml, wherein the aggregates are less than or equal to about 100 microns in diameter, and wherein the drug:

(i) has a surface modifier adsorbed on the surface thereof, and

(ii) has an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(b) a non-aqueous propellant,

wherein the dry powder aggregates and non-aqueous propellant are formulated into a dry powder aerosol for use in a propellant-based pMDI.

40. (Twice Amended) A method of making [a dry powder nanoparticulate drug] an aerosol composition comprising:

(b) forming an aqueous nanoparticulate dispersion of a poorly soluble drug, wherein:

(i) the dispersion comprises poorly soluble crystalline drug particles and a surface modifier adsorbed on the surface thereof, wherein by "poorly soluble" it is meant that the drug has a solubility in the liquid dispersion medium of less than about 10 mg/ml, and

(ii) the drug particles have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm; [and]

(b) spray-drying the nanoparticulate dispersion to form a dry powder of aggregates of the nanoparticulate drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns; and

(c) formulating the dry powder aggregates into an aerosol composition.

42. (Twice Amended) A method of making [a dry powder nanoparticulate drug] an aerosol [formulation] composition comprising:

(b) milling under non-pressurized conditions in a non-aqueous medium having a high boiling point the following:

(i) a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in the non-aqueous medium of less than about 10 mg/ml, and

(iii) a surface modifier, to obtain a nanoparticulate drug composition having an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, [and]

(b) evaporating the non-aqueous medium to obtain a dry powder of aggregates of drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns; and

(c) formulating the dry powder aggregates into an aerosol composition.

43. (Twice Amended) A method of making [a nanoparticulate drug] an aerosol [formulation] composition comprising:

(a) milling under pressurized conditions in a non-aqueous medium the following:

(i) a poorly soluble crystalline drug, wherein by "poorly soluble" it is meant that the drug has a solubility in the non-aqueous dispersion medium of less than about 10 mg/ml, and

(ii) a surface modifier, to obtain a drug having an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm; [and]

(b) evaporating the non-aqueous medium to obtain a dry powder of aggregates of drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns; and

(c) formulating the freeze-dried powder aggregates into an aerosol composition.

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44. (Twice Amended) A method of making [a dry powder nanoparticulate drug] an aerosol composition comprising:

(b) forming an aqueous nanoparticulate dispersion of a poorly soluble drug, wherein:

(i) the dispersion comprises poorly soluble crystalline drug particles, wherein by "poorly soluble" it is meant that the drug has a solubility in the liquid dispersion medium of less than about 10 mg/ml, and wherein the drug particles have an effective average particle size of less than about 1000 nm, meaning at least 50% of the drug particles have a particle size of less than about 1000 nm, and

(ii) a surface modifier adsorbed on the surface thereof; [and]

(b) freeze-drying the nanoparticulate dispersion to form a dry powder of aggregates of the nanoparticulate drug and surface modifier particles, wherein the aggregates have a diameter of less than or equal to about 100 microns; and

(c) formulating the freeze-dried powder aggregates into an aerosol composition.

65. (Amended) The [aerosol composition] method of claim 42, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

66. (Amended) The [aerosol composition] method of claim 42, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.

67. (Amended) The [aerosol composition] method of claim 43, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

68. (Amended) The [aerosol composition] method of claim 43, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.

69. (Amended) The [aerosol composition] method of claim 44, wherein at least 70% of the drug particles have a particle size of less than about 1000 nm.

70. (Amended) The [aerosol composition] method of claim 44, wherein at least 90% of the drug particles have a particle size of less than about 1000 nm.